**Remarks**

Prior to entry of this amendment, claims 1-21 and 29-34 were pending in the application. Claims 1, 2, 5, 11-12, 15, 18, 29, 30, 32 and 33 are amended herein. Claim 1 is amended herein to incorporate the limitations of claims 3 and 5. Claim 2 is amended herein to incorporate the limitations of claim 3. Claims 11-12 and 18 are amended herein to correct form. Claim 15 is amended to depend from claim 4. Claim 29 is amended herein to incorporate the limitations of claims 20 and 34. Claims 5, 32 and 33 are amended herein to correct dependency. Claims 3, 16, 31, and 34 are canceled herein. New claim 35 is added herein. Support for new claim 35 can be found throughout the specification, for example on page 25, lines 18-29.

Thus, after entry of this amendment, **claims 1-2, 4-15, 17-21, 29-30, 32-33, and 35 are pending.** Reconsideration of the subject application is respectfully requested.

*Claim Objections*

Claim 3 is objected to for including a typographical error. Claim 3 is canceled herein, rendering the objection moot.

*Interview Summary*

Applicants thank the Examiner and the Primary Examiner for the helpful interview of October 31, 2006, wherein the rejection under 35 U.S.C. § 103 was discussed. Submitted herewith is a Declaration of Dr. Martin and McFarland Under 37 C.F.R. § 1.132 (signed by Dr. McFarland only). If any minor matters remain prior to allowance of the application, Examiner Seharaseyon is requested to contact the undersigned for a supplemental telephone conference.

The undersigned will submit an executed copy of this Declaration signed by Dr. Martin upon receipt.

*Rejections under 35 U.S.C. § 112, Second Paragraph*

Claims 1-21 and 29-34 are rejected under 35 U.S.C. § 112, first paragraph as allegedly "ameliorating a sign" is not defined in the specification. Applicants respectfully disagree with this assertion.

The specification at page 21, lines 3-10 defines the signs and symptom of multiple sclerosis. A sign of multiple sclerosis is disclosed to be an objective indication of the disease, including "any measurable parameters such as tests for immunological status or the presence of lesions in a subject with multiple sclerosis." "Undesirable signs" are disclosed to be the clinical manifestations of abnormal laboratory results, or medical diagnoses noted by medical personnel, or symptoms reported by the subject that have worsened (see the specification at page 7, lines 29-33). Given the clear definitions provided in the specification, and the high level of one of skill in the art, applicants submit that the metes and bounds of the phrase "amelioriating a sign" are clear and definite.

However, to advance prosecution, and to reduce costs, claim 1 is amended herein to no longer recite "a sign." Applicants believe the amendment of the claim renders the rejection moot without changing the scope of the claim. Applicants expressly reserve the right to prosecute any deleted subject matter in a continuation application.

Claims 11 and 12 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being unclear as to whether the subject is further treated with an interferon. Claims 11 and 12 have been amended to clarify that the subject has failed to respond to treatment with interferon 1a and interferon 1b, respectively, rendering the rejection moot.

Claim 32 is rejected under 35 U.S.C. § 112, second paragraph as allegedly not further limiting the subject matter of claim 4. Claim 32 has been amended to depend from claim 1, thereby rendering the rejection moot.

**Rejections Under 35 U.S.C. § 112, first paragraph**

Claims 1-4, 7, 8, 10-18, 20, 29 and 30 were rejected under 35 U.S.C. § 112, first paragraph as allegedly the use of any antagonist for the treatment of multiple sclerosis is not enabled by the specification. Applicants respectfully disagree with this assertion.

The Office action states that "the specification, while being enabling for a method of treating multiple sclerosis (ameliorating a symptom or by decreasing the number of contrast enhancing lesions as evaluated by MRI), specifically by administering a IL-2 receptor antagonist that is an antibody (drawn to p55 or p75 subunits) composition...." Thus, solely to advance

prosecution, the claims are amended herein to methods for treating multiple sclerosis that utilize antibodies that specifically bind the p55 or p75 subunit of the IL-2 receptor. Applicants submit that the amendment of the claims to be limited to subject matter considered by the U.S. Patent and Trademark Office to be fully enabled by the specification renders the rejection moot. Applicants expressly reserve the right to pursue any additional subject matter in a continuation application.

Claims 32-34 are rejected under 35 U.S.C. § 112, first paragraph as allegedly the use of human monoclonal antibodies is not disclosed in the specification, and constitutes new matter. Claim 34 is canceled herein. Applicants respectfully disagree with this rejection as applied to claims 32 and 33.

The specification states on page 23, lines 17-19 (emphasis added):

> In one specific non-limiting example, the IL-2 receptor antagonist is an antibody, such as a monoclonal antibody, e.g., a chimeric, humanized or *human monoclonal antibody.*

The specification further describes that human antibodies, including fragments of human antibodies, are of use in the claimed methods (see for example, page 25, lines 1-4). The specification further describes the use of a specific human anti-p55 monoclonal antibody, namely huMax-Tac (see the specification at page 8, lines 17-20). Thus, the use of human monoclonal antibodies is clearly not new matter. Reconsideration and withdrawal of the rejection is respectfully requested.

*Rejections Under 35 U.S.C. § 103(a)*

Claims 1-9, 15-19, 21 and 29-31 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over "Study of Zenapax" in view of Light et al.

Light et al. describe dosing regimens for the treatment of transplant rejection using antibodies that bind the IL-2 receptor. Light et al. does not describe the treatment of subjects with multiple sclerosis, let alone the treatment of subjects with multiple sclerosis that have failed to respond to treatment with interferon beta or treatment with an antibody that binds the IL-2 receptor in the absence of treatment with interferon beta. Light et al. describes a number of dosing protocols for the treatment of transplant rejection.

The Office action states that "Study of Zenapax" describes the use of Zenapax in patients with multiple sclerosis who have had at least one relapse in 18 months. The Study was designed to include Zenapax in the treatment of these subjects undergoing treatment with interferon beta. As noted in the Office action, no specific dosing regimen is described.

The "Study of Zenapax" was an initial call for subjects from the present inventors. This abstract describes the use of Zenapax in subjects undergoing concurrent treatment with interferon beta. The Declaration of Drs. Martin and McFarland under 37 C.F.R. § 1.132 describes the protocol summarized in Study of Zenapax.

The results presented in Figs. 3-9 are for subjects originally treated with the "Study for Zenapax" protocol. As disclosed in the specification, see examples 1-5, a number of subjects were treated with Zenapax and interferon beta. This treatment was then discontinued, and the subjects were treated with Zenapax in the absence of interferon beta. The results obtained for one subject, who was treated using the combined treatment (as described in "Study of Zenapax"), and then was treated using only Zenapax (in the absence of interferon) are shown in Fig. 2. Fig. 2 is a graph of the new, total, and supertotal lesions in a subject from the trail design of "Study of Zenapax." The subject was not responding to treatment with interferon (see the left side of the figure, lesions during the period of six months prior to the onset of therapy). Thus, the "Study of Zenapax" treatment protocol, that utilized both interferon-beta and Zenapax, was initiated (see the middle of the figure, lesions during the period of zero to six months of Zenapax treatment). The "Study of Zenapax" protocol was completed at approximately six months. Following this period the subject was treated with Zenapax alone, in the absence of treatment with interferon beta. A unexpectedly superior response was seen in this subject when only Zenapax (in the absence of concurrent treatment with interferon) was used: there were no new lesions during a nine-month period, and the supertotal of lesions remained at zero for the complete study period. Thus, an unexpectedly superior result was obtained when the subject was treated with only Zenapax.

A similar result was obtained in a second subject (see Fig. 1). The results obtained during the initial treatment period (using the treatment protocol as described in the "Study of Zenapax") are shown to the left of the vertical line. When the subject was treated under the "Study of Zenapax" protocol, new lesions developed, and the total number of lesions fluctuated. Following the "Study of Zenapax" protocol, when the subject was treated with Zenapax alone

(see the results to the right of the vertical line), the new and total lesions dropped to zero. Thus, an unexpectedly superior result was obtained using treatment with Zenapax alone (in the absence of treatment with interferon beta).

The Declaration of Drs. Martin and McFarland under 37 C.F.R. § 1.132 describes a clinical study that utilized Zenapax (daclizumab) in the absence of concurrent treatment with interferon beta (termed "daclizumab monotherapy") for the treatment of subjects with multiple sclerosis. As described in the Declaration, daclizumab monotherapy was highly efficacious in 9/13 MS patients. The study documented that daclizumab monotherapy was a well tolerated and highly effective therapeutic option in patients with high-inflammatory MS (who had suboptimal clinical response to interferon beta).

Thus, the studies and results presented in Examples 1-5 and FIGS. 1-2 document that treatment of the subject with multiple sclerosis using daclizumab alone (in the absence of interferon-beta) provides an unexpectedly superior results namely a complete absence of new lesions, and a decrease in the total number of lesions in the brain. The studies and results presented in the accompanying Declaration of Drs. Martin and McFarland confirm the superior results obtained with daclizumab monotherapy. Applicants submit that the showing of an unexpectedly superior result overcomes any *prima facie* case of obvious over Study of Zenapax in combination with Light et al. Reconsideration and withdrawal of the rejection is respectfully requested.

*Co-pending Applic*ation

U.S. Patent Application No. 10/519,311 is co-pending, and is under examination by Examiner Hissong. An Information Disclosure Statement is submitted herewith to make the references cited in the co-pending application of record in the present application.

*Obviousness-Type Double Patenting*

Claims 1-21 and 29-34 were provisionally rejected on the ground of non-statutory obviousness-type double patenting over claim 20 of co-pending U.S. Application No. 10/519,311 (hereinafter the '311 application). Claim 20 of the '311 application has been amended to be directed to a method of treating a subject that has multiple sclerosis that includes (1) administering to a the subject that has multiple sclerosis daclizumab at a dose of 1 to 2 mg/kg for

every other week for two weeks and then monthly and (2) administering to the subject interferon beta-1b at a dose of 0.006 mg to 2 mg by subcutaneous injection every other day, wherein the subject has been previously treated with interferon-beta alone and has failed to respond to treatment with interferon-beta alone. Thus, claim 20 of the '311 application is directed to combined therapy using both daclizumab and interferon beta. As claims 1-21 and 29-34 of the present application are directed to methods for treating multiple sclerosis *in the absence of treatment with beta interferon*, the pending claims are not obvious over claim 20 of the '311 application.

In view of the amendment to claim 20 of the '311 application, reconsideration and withdrawal of the rejection is respectfully requested.

## Conclusion

Applicants respectfully request a telephone conference to discuss the outstanding rejections. Applicants believe that the present application is in condition for allowance, and such action is requested.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By _____
Susan Alpert Siegel, Ph.D.
Registration No. 43,121